



Congenital Diaphragmatic Disease: An Unusual Presentation in Adulthood

Angela Gurrado^{1*}, Roberta Maria Isernia¹, Alessandro De Luca¹, Valentina Ferraro¹, Daniela Virgintino², Anna Napoli³, Giuseppe Cavallaro⁴, Eugenio Maiorano³, Angela Pezzolla⁵ and Mario Testini¹

¹Department of Biomedical Sciences and Human Oncology, Unit of Endocrine, Digestive and Emergency Surgery, University Medical School "A. Moro", Bari, Italy

²Department of Basic Medical Sciences, Neurosciences, and Sensory Organs, Human Anatomy and Histology Unit, University Medical School "A. Moro", Bari, Italy

³Department of Pathology, University Medical School "A. Moro", Bari, Italy

⁴Department of Surgery "P. Valdoni", Sapienza University, Rome, Italy

⁵Department of Emergency and Organs Transplantation, University Medical School "A. Moro", Bari, Italy

Abstract

Congenital Diaphragmatic Disease (CDD) is a relatively common condition that usually occurs in the neonatal period, and the diagnosis of CDD in adulthood is rare. A 64-years-old Caucasian woman was admitted in emergency at our Academic Department, due to a bowel obstruction and dyspnea. The anamnesis revealed intellectual disability and strabismus. A CT scan showed a diaphragmatic herniation in the left area, with chest dislocation of dilated transverse and descending colon, with complete atelectasis of the medial-basal part of the lung. A toxic megacolon was also supposed. Moreover, the left hepatic lobe was not radiologically detectable. An emergency laparotomy was performed, confirming the preoperative diagnosis of toxic megacolon, in the absence of a true diaphragmatic hernia, and a left diaphragm and left liver hypoplasia were reported. An intraoperative bronchoscopy revealed concomitant hypoplasia of the left lung. A subtotal colectomy with ileo-rectal anastomosis was performed. The postoperative course was uneventful. Histological examination demonstrated hyperplasia of the *muscularis mucosae* of the colon and cytoplasmic vacuolization of the *Auerbach plexus ganglia*. The karyotype genetic analysis excluded concomitant microdeletion or duplication syndromes. In conclusion, the correct development of the diaphragm is essential for the neighboring organs; the observed clinical pattern could be related to a partial modification of neural crest cell detachment or migration, which could have been responsible for bowel and diaphragm defects. Even though it was not included in typical neural crest cell syndromes. Further researches should be performed in order to define the sporadic or syndromic source of these multiorgan defects.

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*Correspondence:

Angela Gurrado, Digestive and Emergency Surgery Unit, Department of Biomedical Sciences and Human Oncology, University of Bari. Policlinico of Bari, Piazza Giulio Cesare 11, 70124 Bari, Italy,

E-mail: angelagurrado@libero.it

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Introduction

Congenital Diaphragmatic Disease (CDD) is a relatively common condition that usually occurs in the neonatal period, with an incidence of less than one per 25,000 births [1]; therefore the diagnosis of CDD in adulthood is rare. In some cases, CDD can be a late presenting event (5-25%) [2] Often detected as an incidental findings by routine chest x-ray or abdomen US. Usually, the diagnosis in adults is related to symptoms due to complications, such as respiratory failure, gastric volvulus, bowel occlusion, or perforation, with peritonitis or necrosis [3]. Although the survival of patients with the late-presenting CDD is typically excellent [2], the prognosis may be compromised due to complications. CDDs are currently considered in one of several "classical" sites, such as postero-lateral (*Bochdalek*) [4-6] anterior (*Morgagni*) [4-6] and central and anterior (*Cantrell*) [7] localizations. The genetic contribution to most diaphragmatic defects are complex; even though the gene identification facilitates the understanding of the genotype groundwork and the phenotype outcome, the real pathogenetic mechanism of CDD is still largely unknown. We report a case of a 64-year-old woman treated in emergency for toxic megacolon, with intraoperative diagnosis of hemidiaphragm hypoplasia.

Case Presentation

A 64-years-old Caucasian woman was admitted in emergency at our Academic Department with dyspnea and persistent respiratory failure, cough, general weakness, bowel obstruction with

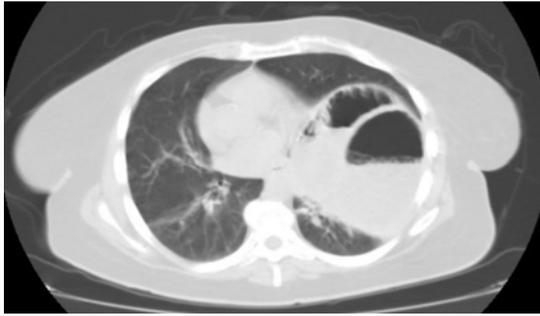


Figure 1: Thorax-abdominal CT-scan showed a diaphragmatic herniation of the left side with chest dislocation of an extremely dilated transverse and descending colon. In addition to this consensual complete atelectasis of the medial-basal part of the lung, and a right deviation of the mediastinal structures.

abdominal distention and severe pain. The patient showed also intellectual disability, associated with an unusual facial appearance, a heterochromia iridum and a monolateral corneal defect, disproportionate short stature and retarded skeletal maturation; nevertheless, this cohort of clinical signs was not included in the known classical congenital syndromes. Blood investigations were normal, except for a moderate hydro-electrolyte disorder; the hemogasanalysis demonstrated a severe hypoxia. A chest X-ray, confirmed by thorax-abdominal CT-scan (Figure 1), showed a diaphragmatic herniation of the left side with chest dislocation of an extremely dilated transverse and descending colon. In addition to this consensual complete atelectasis of the medial-basal part of the lung, and a right deviation of the mediastinal structures. A toxic megacolon was also supposed. Moreover, the left hepatic lobe was not radiologically detectable.

Therefore, an emergency laparotomy was performed, confirming the preoperative diagnosis of toxic megacolon, with marked distention of the colon (diameter >10 cm) in the absence of a true diaphragmatic hernia. The transverse and left large bowel, as well as, the spleen appeared dislocated, indeed, in the left chest, in the presence of the lifting of hypoplastic left diaphragm, and not of the herniation through a diaphragmatic solution of continuity (Figure 2). Furthermore, the abdominal exploration showed hypoplasia of the left hepatic lobe, and a dysmorphic gallbladder. An intra-operative bronchoscopy with *Carlens's* tube revealed hypoplasia of the left bronchial system and the absence of the left basal lobe. A sub-total colectomy with mechanical ileo-rectal anastomosis, splenectomy, and temporary ileostomy were performed. Histological examination demonstrated a marked hyperplasia of the *muscularis mucosae* of the colon and cytoplasmic vacuolization of the *Auerbach plexus ganglia*. The karyotype genetic analysis excluded concomitant microdeletion or duplication syndromes. The postoperative course was uneventful and the patient was discharged on the 10th post-operative day. Two months after the first operation the patient underwent ileostomy closure.

Discussion

To our knowledge, this is the first reported case of toxic megacolon in a patient with congenital hypoplasia of the left bronchial-lung system, of the left liver, with dysmorphism of the gallbladder, and of the left diaphragm. In the current case, we suspected an origin of the CDD to be different from the common congenital diaphragmatic hernia; as it seemed to be related to a multi-organ embryological

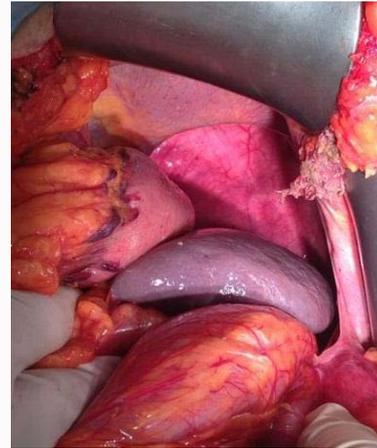


Figure 2: The transverse and left large bowel, as well as, the spleen appeared dislocated in the left chest, in the presence of the lifting of hypoplastic left diaphragm, and not of the herniation through a diaphragmatic solution of continuity.

mistake of development. The diaphragmatic muscle is a complex structure that develops around the third-fourth month of gestation from several embryonic structures: the *septum transversum* sets into a central tendon; the pleuro-peritoneal membranes form the muscular components; consequently, the diaphragm external border takes its origin from mesodermal tissues of the thoracic wall [8,9]. Finally, the left and the right *crura* develop from the dorsal esophageal mesentery, and they are included in the dorso-medial part of the dome shaped muscle [10,11]. Correct development of the diaphragm is essential for the neighboring organs. In the third week of gestation, the foregut endoderm differentiates into epithelial cell types that form the lungs and the trachea [12]. The lung mesenchyme, instead, originates from the lateral plate of the mesoderm, and develops into several lung components, including connective tissue, smooth muscle surrounding the airways and blood and lymphatic vessels, tracheal cartilages and pleura [13]. In particular, the lung begins to grow as a ventral outpouching on the floor of the primitive foregut and their development may be divided into two phases: (1) embryonic, which corresponds to formation of bronchial buds, and (2) fetal, which includes four stages, pseudoglandular, acinar/canalicular, saccular, and alveolar. Many factors may influence the normal lung development, including the normal fetal breathing movements [14-16], the appropriate volumes of extra- and intrapulmonary fluids [17], the pulmonary blood flow [18], and, in particular, an adequate intrathoracic space [12-19]. During the phase of lung formation (8th - 28th week of fetal development), the branches of bronchial buds form the respiratory trees. Around the 10th week, the midgut retracts into the abdomen and rotates. In this reported case, we assume that, during these weeks of fetal development, the large intestine, still not fixed to the body wall and under the pressure of the others growing organs (mainly the liver and the elongating ileum), grows towards the left thoracic cavity, partially invading it and inhibiting the normal lung growth, due to the hemidiaphragm hypoplasia. The pathogenetic hypothesis, therefore, to explain the reported left bronchial system hypoplasia was due to the lack of space for the lung germ to spread out, caused by compression from underneath bowel mass. The latter, the diaphragm may have been stretched over time and reduced to a thin rim of tissue, mostly fibrotic at gross inspection, unable to perform the muscular functions. Considering the liver development, the first morphological sign is formation of the hepatic diverticulum,

constituted by an epithelial thickening of the ventral foregut, adjacent to the developing heart [20]. The anterior portion of the hepatic diverticulum gives rise to the liver and intrahepatic biliary tree, while the posterior portion forms the gallbladder and extra-hepatic bile ducts [21,22]. The hepatic endodermal cells, known as hepatoblasts, delaminate from the epithelium and invade the adjacent *septum transversum* mesenchyme to form the liver bud [23]. Consequently, the correct growth of the liver depends on the correct position of all surrounding organs, in particular of the diaphragm [24]. In the current case, therefore, the hypoplastic left lobe of the liver and the dysmorphic gallbladder may be the result of incorrect development from an originally unaltered embryonic liver, because of hypoplastic or a dislocated diaphragm. In this view, an alternative pathogenetic hypothesis, that put together the observed diaphragmatic hypoplasia and the presence of megacolon, regards a possible defect in neural crest cells migration. The alteration of this phenomenon was involved in several well known syndromes, likewise *Peter's* anomaly [25], but it may also include a variable degree of mental retardation, unusual facial appearance, eye defects, disproportionate short stature, retarded skeletal maturation, and visceral anomalies. In addition to this an unusual facial appearance, our patient presented a heterochromia iridium and a monolateral corneal defect, which are wholly suggestive of a *Peter's* like anomaly. The observed clinical pattern could be related to a partial modification of neural crest cell detachment or migration, then responsible for both bowel and diaphragm defects, although it was not included in typical neural crest cell syndromes. This hypothesis is supported by the histological report of the *Auerbach plexus ganglia* alteration and by recent data [26,27] on diaphragmatic development. It has been recently demonstrated, indeed, that, in early mouse embryos, the *alpha4-Integrin* is expressed in a subset of neural crest cells and in epicardial progenitor cells [26]; in addition, this gene is involved in the development of *septum transversum*. This suggests the role of the subset of neural crest cells of *septum transversum* to provide the muscle and tendon components of the adult diaphragm [27].

Conclusion

To summarize, the described multiorgan alterations could have been founding their origin in the hypoplasia and dislocation of the left hemidiaphragm, maybe sustained by or associated with an alteration of the neural crest cells migration during the embryological development. CDD could be caused by several genetic alterations, though their original molecular and genetic mechanisms are mostly unknown. The diagnosis could be rarely achieved in the adulthood, because of the absence of symptoms, but the morbidity could increase dramatically when triggering events occur, such toxic megacolon in the current case, thus revealing other possible embryonic developmental alterations.

References

- Akinkuotu AC, Cruz SM, Cass DL, Cassady CI, Mehollin-Ray AR, Williams JL, et al. Revisiting outcomes of right congenital diaphragmatic hernia. *J Surg Res.* 2015;198(2):413-7.
- Topor L, Patrancus T, Caragata R, Moga A. Left congenital diaphragmatic hernia- case report. *Chirurgia (Bucur).* 2015;110(1):84-7.
- Losty PD. Congenital diaphragmatic hernia: where and what is the evidence? *Semin Pediatr Surg.* 2014;23(5):278-82.
- Irish MS, Holm BA, Glick PL. Congenital diaphragmatic hernia. A historical review. *Clin Perinatol.* 1996;23(4):625-53.
- Al-Salem AH. Bilateral congenital Morgagni-Larrey's hernia. *World J Pediatr.* 2010;6(1):76-80.
- Stokes KB. Unusual varieties of diaphragmatic herniae. *Prog Pediatr Surg.* 1991;27:127-47.
- Wesselhoeft CW Jr, DeLuca FG. Neonatal septum transversum diaphragmatic defects. *Am J Surg.* 1984;147(4):481-5.
- Perry SF, Similowski T, Klein W, Codd JR. The evolutionary origin of the mammalian diaphragm. *Respir Physiol Neurobiol.* 2010;171(1):1-16.
- Iritani I. Experimental study on embryogenesis of congenital diaphragmatic hernia. *Anat Embryol (Berl).* 1984;169(2):133-9.
- Dietrich S, Abou-Rebyeh F, Brohmann H, Bladt F, Sonnenberg-Riethmacher E, Yamaai T, et al. The role of SF/HGF and c-Met in the development of skeletal muscle. *Development.* 1999;126(8):1621-9.
- Bladt F, Riethmacher D, Isenmann S, Aguzzi A, Birchmeier C. Essential role for the c-met receptor in the migration of myogenic precursor cells into the limb bud. *Nature.* 1995;376(6543):768-71.
- Warburton D, El-Hashash A, Carraro G, Tiozzo C, Sala F, Rogers O, et al. Lung organogenesis. *Curr Top Dev Biol.* 2010;90:73-158.
- Hong KU, Reynolds SD, Watkins S, Fuchs E, Stripp BR. In vivo differentiation potential of tracheal basal cells: evidence for multipotent and unipotent subpopulations. *Am J Physiol Lung Cell Mol Physiol.* 2004;286(4):L643-9.
- Featherstone NC, Connell MG, Fernig DG, Wray S, Burdya TV, Losty PD, et al. Airway smooth muscle dysfunction precedes teratogenic congenital diaphragmatic hernia and may contribute to hypoplastic lung morphogenesis. *Am J Respir Cell Mol Biol.* 2006;35(5):571-8.
- Featherstone NC, Jesudason EC, Connell MG, Fernig DG, Wray S, Losty PD, et al. Spontaneous propagating calcium waves underpin airway peristalsis in embryonic rat lung. *Am J Respir Cell Mol Biol.* 2005;33(2):153-60.
- Miller AA, Hooper SB, Harding R. Role of fetal breathing movements in control of fetal lung distension. *J Appl Physiol.* 1993;75(6):2711-7.
- Souza P, O'Brodovich H, Post M. Lung fluid restriction affects growth but not airway branching of embryonic rat lung. *Int J Dev Biol.* 1995;39(4):629-37.
- Que J, Wilm B, Hasegawa H, Wang F, Bader D, Hogan BL. Mesothelium contributes to vascular smooth muscle and mesenchyme during lung development. *Proc Natl Acad Sci USA.* 2008;105(43):16626-30.
- Ingber DE. Mechanobiology and diseases of mechanotransduction. *Ann Med.* 2003;35(8):564-77.
- Si-Tayeb K, Lemaigre FP, Duncan SA. Organogenesis and development of the liver. *Dev Cell.* 2010;18(2):175-89.
- Vestentoft PS, Jelnes P, Hopkinson BM, Vainer B, Møllgård K, Quistorff B, et al. Three-dimensional reconstructions of intrahepatic bile duct tubulogenesis in human liver. *BMC Dev Biol.* 2011;11:56.
- Roskams T, Desmet V. Embryology of extra- and intrahepatic bile ducts, the ductal plate. *Anat Rec (Hoboken).* 2008;291(6):628-35.
- Godlewski G, Gaubert-Cristol R, Rouy S, Prudhomme M. Liver development in the rat and in man during the embryonic period (Carnegie stages 11-23). *Microsc Res Tech.* 1997;39(4):314-27.
- Ntlhe LM, Mokotedi TD. Congenital hepatophrenic fusion: septum transversum-liver primordium anomaly. *S Afr J Surg.* 2007;45(1):28-30.
- Ni W, Wang W, Hong J, Zhang P, Liu C. A novel histopathologic finding in the Descemet's membrane of a patient with Peters Anomaly: a case-report and literature review. *BMC Ophthalmol.* 2015;15:139.
- Pinco KA, Liu S, Yang JT. alpha4 integrin is expressed in a subset of cranial neural crest cells and in epicardial progenitor cells during early mouse

- development. *Mech Dev.* 2001;100(1):99-103.
27. Pober BR, Russell MK, Ackerman KG. Congenital diaphragmatic hernia overview. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJH, editors. *GeneReviews*[®] [Internet]. Seattle (WA): University of Washington, Seattle. 1993-2017.